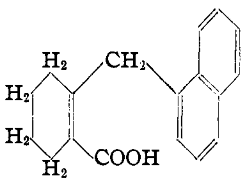
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

1',2',3',4'-Tetrahydro-10-isopropyl-1,2-benzanthracene

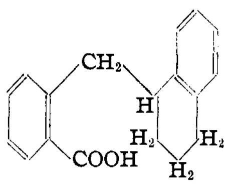
BY LOUIS F. FIESER AND E. B. HERSHBERG[1]

In our paper describing the preparation of a number of 10-alkyl-1,2-benzanthracenes by the addition of Grignard reagents to 1,2-benz-10-anthrone and dehydration of the resulting carbinols,[2] we reported a curious observation for which we had no adequate explanation. The product obtained from the interaction of isopropylmagnesium chloride and one of several preparations of the crude anthrone had the composition not of the expected 10-isopropyl-1,2-benzanthracene but of a tetrahydro derivative of this substance. The new hydrocarbon yielded 10-isopropyl-1,2-benzanthracene on dehydrogenation with sulfur, whereas with selenium the *meso*-alkyl group was eliminated and the product was 1,2-benzanthracene. It seemed unlikely that an extensive reduction had occurred in the course of the Grignard reaction, and indeed in further experiments carried out under similar conditions but with different preparations of the anthrone the only hydrocarbon isolated was the normal product, 10-isopropyl-1,2-benzanthracene.

As we noted briefly in our first report, a later observation suggested that the reduction encountered in the one isolated case had occurred at an earlier stage of the synthesis. The 1,2-benz-10-anthrone employed was obtained from 2-(α-naphthylmethyl)-benzoic acid, which we prepared conveniently, and usually in yields over 80%, by the high pressure hydrogenation of 2-(α-naphthoyl)-benzoic acid using copper chromite catalyst (37-KAF). The reduction of the carbonyl group by this method proceeds so smoothly that we sometimes employed the extracted acid directly without further purification. In the experiment in question, however, the pressure drop was about 28% greater than usual and the reaction product clearly contained more than one substance. On fractional crystallization there was isolated a new acid having the composition of a tetrahydro derivative of the normal reaction product. Any one of the three aromatic rings of the starting material might conceivably suffer hydrogenation, as in formulas I–III. The second of these structures is eliminated by the observation that the acid can be cyclized to an anthrone-like substance, and the further fact that this on oxidation yields a quinone which gives the vat test characteristic of anthraquinones excludes formula I. The remaining formula (III) is alone consistent with the properties noted, and this structure for the hydrogenation product was definitely established by synthesis. The keto acid (IV) obtained from α-tetralylmagnesium bromide and phthalic anhydride yielded on reduction, either with zinc and alkali or by high pressure hydrogenation, an acid identical with the substance under discussion. It is therefore established that when the high pressure hydrogenation of 2-(α-naphthoyl)-benzoic acid (V) proceeds beyond the stage of reduction of the carbonyl group to give VI, the unsubstituted ring of the naphthalene nucleus is attacked, yielding 2-(α-tetralylmethyl)-benzoic acid (III).



I



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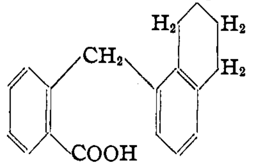
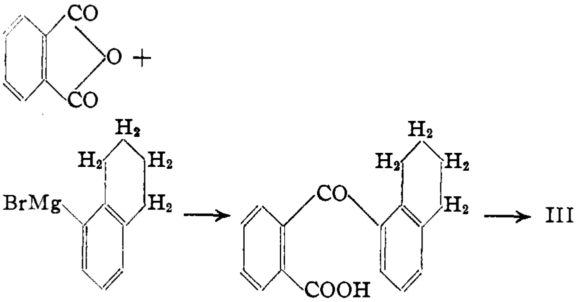


III



IV

Although there is no mention in the literature of the tetrahydro acids III and IV as such, Willstätter and Waldschmidt-Leitz[3] described two

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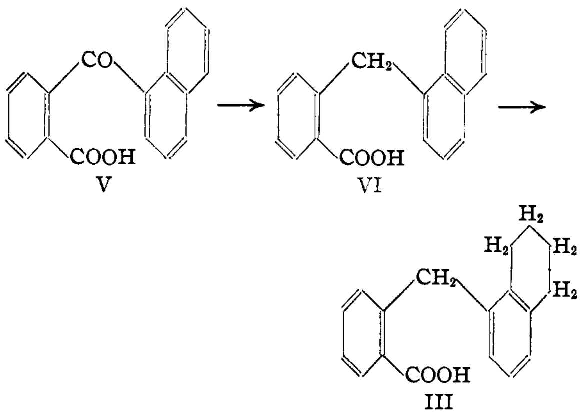
(3) Willstätter and Waldschmidt-Leitz, *Ber.*, **54**, 1420 (1921).

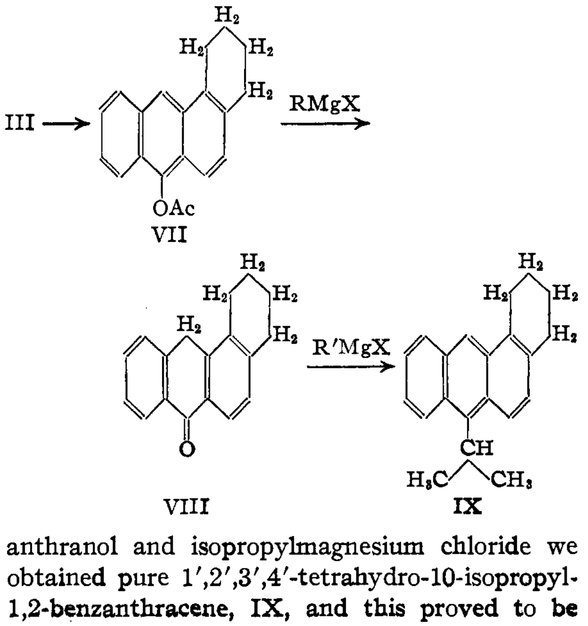


substances which correspond rather closely in melting point with our acids. These were isolated as intermediate products in the exhaustive hydrogenation of 2-(α-naphthoyl)-benzoic acid (V) and 2-(α-naphthylmethyl)-benzoic acid (VI), respectively, and they were regarded by the German investigators as dihydro derivatives. This conclusion, however, was based largely upon the analytical data, and an inspection of the figures will show that their analyses agree almost as well with the formulas for tetrahydrides as for dihydrides. Because of this uncertainty, and in view of the correspondence in properties of the supposed dihydro compounds with our tetrahydrides, we repeated the low pressure hydrogenations, using Adams catalyst activated with ferrous chloride, and conducting the reductions in glacial acetic acid. Both acids slowly absorbed hydrogen, and in accordance with the observations of Willstätter and Waldschmidt-Leitz the reduction proceeded much more slowly with the naphthylmethylbenzoic acid (VI) than with the keto acid (V). The two products proved to be identical with the synthetic 2-(α-tetraloyl)-benzoic acid (IV) and 2-(α-tetralylmethyl)-benzoic acid (III) described above. The empirical formulas suggested by Willstätter and Waldschmidt-Leitz are thus in error, and it is now clear that the hydrogenation of the aromatic ring does not in these cases lead to the intermediate formation of dihydro compounds but proceeds normally to the tetrahydride stage.

ACIDS OF WILLSTÄTTER AND WALDSCHMIDT-LEITZ

	From V		From VI	
	% C	% H	% C	% H
Calcd. for dihydride	77.67	5.07	81.78	6.11
Calcd. for tetrahydride	77.13	5.75	81.19	6.80
Found	77.42	5.45	81.78 (Av.)	6.38 (Av.)

Whereas the hydrogenation of 2-(α-naphthoyl)-benzoic acid at low pressure results in the saturation of an aromatic ring, the first step in the high pressure reaction in the presence of base-metal catalyst consists in the reduction of the carbonyl group, for when the reaction is stopped at the proper point the naphthylmethylbenzoic acid (VI) is obtained in good yield and purity. There is, therefore, little reason to suppose that the tetralylmethylbenzoic acid (III) arising in certain of the high pressure experiments is formed by nuclear hydrogenation to IV, followed by reduction of the carbonyl group; acid VI probably suffers hydrogenation at high pressure exactly as it does in the low pressure reaction.



The isolation of 2-(α-tetralylmethyl)-benzoic acid (III) in one hydrogenation experiment made it probable that this acid had been the source of the tetrahydroisopropylbenzanthracene resulting in one case from the Grignard reaction, and in order to test this point the isolated acid was put through the remaining steps of the synthesis. Catalytic cyclization with zinc chloride in acetic anhydride–acid gave the enol acetate VII, and when this was hydrolyzed through the MgX-salt the liberated enol ketonized to VIII in the course of the purification. The tendency to tautomerize is in contrast to the behavior of 1,2-benz-10-anthranol, which is much more stable in the enolic form,[2] and the substance is comparable rather with anthranol. We have found that anthranol prepared in the same way ketonizes during crystallization. From the stable tetrahydrobenz-10-anthranol and isopropylmagnesium chloride we obtained pure 1′,2′,3′,4′-tetrahydro-10-isopropyl-1,2-benzanthracene, IX, and this proved to be identical with the hydrocarbon previously obtained. It is concluded that the Grignard reaction proceeds normally and that the unexpected result in one experiment was due to the use of partially over-hydrogenated material.

As an incidental observation, we may call attention to a discrepancy in the melting point reported by Schroeter[4] for *ang.*-tetralanthraquinone and that found in the present work. Schroeter obtained the substance by fractional crystallization of a mixture of the angular and the (less soluble) linear isomer and reported the melting point 135°, while we prepared the quinone both by the oxidation of the corresponding anthrone VIII and by the cyclization of the keto acid IV with sulfuric acid and the best sample melted at 157.5–158.5°, corr. Since the latter methods present no points of uncertainty, it seems probable that Schroeter's sample was either a mixture or a molecular compound of the angular and linear isomers.

Experimental Part[5]

2-(α-Tetraloyl)-benzoic Acid (IV). (a) Synthesis.—α-Tetralylamine was prepared as described in the literature[6] but more extensively purified. The combined material from 200 g. of α-naphthylamine was submitted to steaming from an acid solution and crystallized as the hydrochloride. The free base, obtained by steam distillation from strong alkali and fractionated in a 3-ft. (91-cm.) column packed with glass helices, boiled at 279.0–279.3° (763 mm.); yield, 89 g. (43%). The amine when warm quickly darkens on exposure to air. In converting the amine (37 g.) into α-bromotetralin,[7] it was found advantageous to add 10–15 g. of copper powder (reduced with hydrogen) to the solution prepared by dissolving in 200 cc. of 48% hydrobromic acid the cuprous bromide from 75 g. of hydrated copper sulfate, 48 g. of potassium bromide, and 15.6 g. of sodium bisulfite. The copper becomes etched and acquires an actively catalytic surface and nitrogen evolution occurs at room temperature. The product from two batches of amine was steam distilled (slow) and the oil was washed in ether with alkali and distilled, giving 55 g. (52%) of α-bromotetralin, b. p. 135–140° at 16 mm.

The Grignard reagent from 29.4 g. of α-bromotetralin and 10 g. of magnesium was added slowly to a vigorously stirred suspension of 35.5 g. of phthalic anhydride in 250 cc. of hot benzene, and after stirring for one and one-half hours on the steam-bath the mixture was poured onto dilute acid and the solvents were removed with steam. The collected solid was treated with dilute soda solution and submitted to steam distillation, and the resulting solution, filtered from undissolved phthalide, was chilled to 10° and stirred into ice-cold acid. This gave a granular product (25.5 g.), m. p. 195–205°, whereas acidification at a higher temperature resulted in the separation of a sticky mass. A solution of the crude product in acetone was treated with benzene and concentrated; when the acetone was largely displaced the product began to crystallize, and 21 g. (54%) of acid, m. p. 205–206°, was obtained. Recrystallization from ethyl acetate gave colorless prisms, m. p. 207–207.5°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.13; H, 5.75. Found: C, 77.46; H, 5.63.

(b) According to Willstätter and Waldschmidt-Leitz.[3]—A solution of 1 g. of α-naphthoylbenzoic acid in 50 cc. of glacial acetic acid was shaken with hydrogen and 0.1 g. of Adams platinum catalyst, activated with 0.25 cc. of 1% ferrous chloride solution. The reaction stopped in ten hours, with the absorption of 1.66 moles of hydrogen. The product was precipitated from the filtered solution with water, and one crystallization from dilute alcohol gave 0.35 g. (34%) of acid, m. p. 190–195°. After three recrystallizations from dilute alcohol and one from benzene, the product melted at 206.5–207.5° and did not depress the melting point of the synthetic acid. Willstätter and Waldschmidt-Leitz[3] report the melting point 201° (uncorr.?).

2-(α-Tetralylmethyl)-benzoic Acid (III). (a) Isolation as By-product.—A 50-g. batch of α-naphthoylbenzoic acid was mixed with 3 g. of catalyst (37-KAF) and submitted to hydrogenation at 175° for five hours. The pressure drop was 280 lb., whereas the average drop previously observed was 220 lb. (theory, 273 lb.). The product (37.3 g.) melted at 148–151°, and as this is close to the value for pure 2-(α-naphthylmethyl)-benzoic acid (148–148.5°) a part of the material was cyclized directly. The material obtained was so poor that 12 g. of the hydrogenation product was carefully crystallized. After nine crystallizations from dilute methanol and one from benzene–ligroin, there was obtained 3.6 g. of apparently homogeneous material melting at 163–163.5°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.19; H, 6.80. Found: C, 81.44; H, 6.93.

It was later found in a cyclization experiment (see below) that this material contained a small amount of 2-(α-naphthylmethyl)-benzoic acid, which may account for the slightly high value found for carbon. The melting point is somewhat lower than that of the pure, synthetic acid.

(b) By Reduction of Synthetic IV with Zinc and Alkali.—A mixture of 2 g. of the keto acid IV, 25 cc. of 2 *N* sodium hydroxide, and 2 g. of zinc dust was heated on the steam-bath for forty-five hours, adding 25 cc. more alkali in portions. The precipitated material was treated with warm bicarbonate solution, which left a residue of undissolved lactone (below), and the acid obtained on acidification was crystallized to constant melting point from dilute methanol. **The 2-(α-tetralylmethyl)-benzoic acid** so prepared formed long, slender, glistening blades, m. p. 166–166.5°; yield 0.88 g. (46%). There was no depression in the melting point on admixture with the material isolated as a by-product (a).

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[4] Schroeter, *Ber.*, **54**, 2242 (1921); German Patent 346,673, Dec., 1921.

[5] All melting points are corrected. Analyses by Mrs. G. M. Wellwood and Mrs. Verna R. Keevil.

[6] Bamberger and Althausse, *Ber.*, **21**, 1786 (1888); Green and Rowe, *J. Chem. Soc.*, **113**, 955 (1918).

[7] Smith, *ibid.*, **85**, 728 (1904).

The lactone, **2-(α-tetralyl)-phthalide** (0.55 g.), crystallized from dilute methanol as glistening blades, m. p. 123.5–124°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.80; H, 6.10. Found: C, 81.66; H, 6.06.

(c) **Best Method of Preparation.**—This consisted in the hydrogenation of 2-(α-tetraloyl)-benzoic acid (29 g.) with copper chromite catalyst (1.6 g.) at 215° and an initial pressure of 2800 lb. (three hours). There was obtained 24.1 g. (94%) of purified acid, m. p. 164.5–165.5°. The yields were even higher in smaller runs.

(d) **According to Willstätter and Waldschmidt-Leitz.**[3]—Hydrogenation of 2-(α-naphthylmethyl)-benzoic acid (3 g.) in glacial acetic acid (50 cc.) with Adams catalyst (0.2 g.), treated with ferrous chloride solution (0.15 cc.) was continued for three days without reactivation of the catalyst. The filtered solution after concentration deposited 2.1 g. (69%) of product, m. p. 161–163°. Further purification brought the melting point to 164–164.5° and mixed melting point determinations established the identity of the substance with the synthetic acid described in the two preceding sections. Willstätter and Waldschmidt-Leitz[3] record the melting point 163° (uncorr.?) for their supposed dihydro compound and state that their sample absorbed bromine but did not decolorize alkaline permanganate. Our pure acid did not react with bromine, even on warming.

1′,2′,3′,4′-Tetrahydro-1,2-benzanthranyl-10-acetate (VII). (a) **Isolation.**—Cyclization of 2.6 g. of the sample of 2-(α-tetralylmethyl)-benzoic acid isolated as a by-product by the method described below (b) gave 2.7 g. of material, m. p. 112–115°. Eight crystallizations from acetic acid, benzene–ligroin, and ligroin brought the melting point of the less soluble fraction to 157–160° (0.2 g.), and this material did not depress the melting point (163–163.5°) of 1,2-benzanthranyl-10-acetate.[2] The more soluble tetrahydro compound in the mother liquors was then obtained in a pure condition with comparative ease; it crystallized from ligroin (b. p. 60–70°) as short, thick, pale yellow prisms, m. p. 117.5–118.5°.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.74; H, 6.24. Found: C, 82.42; H, 6.36.

(b) **Preparation in Quantity.**—The acid III synthesized from α-bromotetralin was cyclized by the method previously developed,[2] 24.1 g. of the acid being refluxed for one hour with a mixture of 150 cc. of glacial acetic acid, 100 cc. of acetic anhydride, and 2 g. of fused zinc chloride. After adding water and cooling, 23.8 g. (90%) of acetate, m. p. 112–114°, crystallized. Recrystallization of a sample from ether–petroleum ether brought the melting point to 116–118°.

1′,2′,3′,4′-Tetrahydro-1,2-benz-10-anthrone (VIII).—For hydrolysis, 8 g. of the above acetate, section (b), m. p. 112–114°, was added to the Grignard solution from 14.8 g. of *n*-butyl bromide, the ether was displaced by benzene and after refluxing for one hour dilute acid was added, the washed organic layer was concentrated and treated with ligroin. The liberated enol appears to ketonize immediately, for the product which separated was the colorless anthrone; yield, 5.6 g. (82%), m. p. 180–181°. Further crystallization gave long, flat, refractive needles, m. p. 181–182°.

The anthrone was first prepared from the crude acetate VII of section (a), m. p. 112–115°, and in this case the small amount of 1,2-benz-10-anthranol present as an impurity was eliminated easily in the first crystallization from benzene, for the substance remains in the more soluble enolic form (orange) and is retained in the mother liquor. The tetrahydro compound after crystallization melted at 181–182°.

Anal. Calcd. for $C_{18}H_{16}O$: C, 87.07; H, 6.49. Found: C, 87.20; H, 6.61.

1′,2′,3′,4′-Tetrahydro-1,2-benzanthraquinone (**ang.-Tetralanthraquinone**).—A solution of 100 mg. of the anthrone VIII in 5 cc. of glacial acetic acid was treated at 50–60° with 60 mg. of chromic anhydride in 3 cc. of dilute acetic acid. Oxidation occurred at once and after refluxing for five minutes the solution was diluted until saturated. The quinone separated on cooling as long, thin, bright yellow blades, m. p. 157.5–159° (80 mg.). The recrystallized product melted at 157.5–158.5°; it gives with alkaline hydrosulfite a red-orange vat which is decolorized by shaking with air.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.43; H, 5.38. Found: C, 82.42; H, 5.63.

A sample of the quinone prepared by the cyclization of 2-(α-tetraloyl)-benzoic acid with concentrated sulfuric acid was somewhat less pure (m. p. 153.2–153.7°) but did not depress the melting point of the above sample. Mixtures of the latter with the material, m. p. 135°, prepared according to Schroeter[4] melted at intermediate temperatures.

1′,2′,3′,4′-Tetrahydro-10-isopropyl-1,2-benzanthracene (IX).—To the Grignard reagent from 3 g. of isopropyl bromide (b. p. 59.3–59.5°) and 0.6 g. of magnesium, 0.89 g. of the anthrone VIII (m. p. 179–181°) was added, the ether of the light green solution was displaced by benzene, and the solution was refluxed for one-half hour and decomposed. The benzene layer was washed, evaporated to dryness on the hot plate, and the yellow oil remaining was taken into benzene and the solution passed through a tower of activated alumina and again evaporated. Crystallization of the product from methanol gave in all 0.66 g. (66%) of product melting from 80 to 82.5°. The best material formed pale greenish-yellow prisms, m. p. 81.9–82.5°, with a strong blue fluorescence by daylight.

Anal. Calcd. for $C_{21}H_{22}$: C, 91.91; H, 8.10. Found: C, 92.00; H, 8.09.

This material differs in crystalline form from the product, m. p. 72.5–73.5°, previously isolated[2] from a mixture and the melting point is considerably higher. Mixtures of the two samples, however, melted at 72.5–80°, and the picrates correspond exactly in properties, that from the new product forming reddish black needles, m. p. 134.5–135°, identical in melting point and mixed melting point with the earlier sample.

It is probable that the impurity responsible for the low melting point of the earlier sample was 10-isopropyl-1,2-benzanthracene and that in the oxidation experiment this substance was the source of the small quantity (13%) of 1,2-benzanthraquinone isolated. The 1,2-benzanthracene obtained on dehydrogenating the hydrocarbon mixture with selenium was formed in such an appreciable amount (36%) that it must have come in large part from the tetrahydro-10-isopropylbenzanthracene present, and in any case the elimination of the *meso*-isopropyl group in the course of the reaction is indicated. An analogous case is reported by Cook,[8] who observed the loss of an isopropyl group from the 5-position in the course of a selenium dehydrogenation.

Summary

Continuation of the high pressure hydrogenation of 2-(α-naphthoyl)-benzoic acid beyond the stage of reduction of the carbonyl group results in the fixation of hydrogen to the unsubstituted ring of the naphthalene nucleus. The structure of the resulting 2-(α-tetralylmethyl)-benzoic acid was established by synthesis. This acid is recognized as the precursor of a tetrahydro-10-isopropyl-1,2-benzanthracene previously isolated and now identified by synthesis as the 1′,2′,3′,4′-tetrahydro compound.

Supposed dihydro derivatives of 2-(α-naphthoyl)-benzoic acid and of 2-(α-naphthylmethyl)-benzoic acid have been identified as tetrahydro compounds, and the *ang.*-tetralanthraquinone of the literature has been shown to be impure.

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[8] Cook, *J. Chem. Soc.*, 1592 (1933).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Convallatoxin

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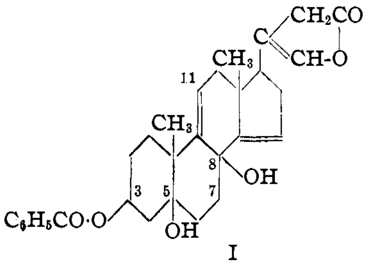
Convallatoxin, the cardiac glycoside isolated by W. Karrer[2] from lily of the valley blossoms, is of particular interest because it surpasses all other known heart poisons in potency.[3] Tschesche and Haupt[4] established for the crystalline glycoside the formula $C_{29}H_{42}O_{10}$ and determined that the sugar component is a methyl pentose very probably identical with *l*-rhamnose. In contrast to the heart poisons which contain 2-desoxy sugars, convallatoxin belongs to the class in which the glycosidic linkage is highly resistant to hydrolysis. After prolonged boiling with aqueous-alcoholic sulfuric acid, Tschesche and Haupt succeeded in eliminating the sugar residue, but the reaction product, isolated as the benzoate, proved to be the monoanhydro derivative of the genin. In the Zerewitinoff test this benzoate liberated two moles of gas, which Tschesche and Haupt took as an indication of the presence of two free tertiary hydroxyl groups. Convallatoxin was found to give the Legal test and to be isomerized by alkali, indicating, respectively, that the glycoside probably contains the unsaturated lactone ring characteristic of the more common plant heart poisons and that a hydroxyl group is present at C_{14} to participate in the isomerization as well as in the establishment of an anhydro linkage during hydrolysis. From the observation that the glycoside absorbs one mole of hydrogen rapidly and a second mole very slowly, Tschesche and Haupt concluded that it contains an inert nuclear double bond in addition to the more active center of unsaturation in the lactone ring. Since anhydroconvallatoxigenin benzoate shows no selective absorption in the ultraviolet, the inert linkage evidently is not conjugated with the anhydro linkage.

From these observations, and on the assumption of the skeletal structure common to the other C_{23}-cardiac aglycones, Tschesche and Haupt suggested for anhydroconvallatoxigenin benzoate the formula I. The location of the nuclear double bond at a bridge head probably would account for its inert character, and the arrangement suggested for the tertiary hydroxyl groups was considered to be consistent with the persistence of these groups during treatment with acid. In a subsequent discussion of the problem, the objection was raised by one of us and Newman[5] that the tertiary hydroxyl group at C_8 would be subject to such



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[1] Du Pont Research Fellow.

[2] W. Karrer, *Helv. Chim. Acta*, **12**, 506 (1929).

[3] K. K. Chen, A. L. Chen and R. C. Anderson, *J. Am. Pharm. Assoc.*, **25**, 579 (1936).

[4] Tschesche and Haupt, *Ber.*, **69**, 459 (1936).

[5] Fieser and Newman, *J. Biol. Chem.*, **114**, 707 (1936).